REMARKS

Discussion of the Status of Claims and Amendments to the Claims

Claims 1-11, 16-26, 31-41, 46-56, 61-71, 76-86, 91-101, 106-107, 110-111, 114-115, 118-119, 122-123, and 126-127 are pending. Applicant elected the subject matter of claims 1-11 and 16-26 for further consideration. Claims 31-41, 46-56, 61-71, 76-86, 91-101, 106-107, 110-111, 114-115, 118-119, 122-123, and 126-127 represent non-elected subject matter. Applicant has amended the non-elected claims so that they depend on the elected claims.

Upon entry of the amendment:

(1) claims 1-5, 16-20, 31-35, 46-56, 61-65, 76-80, 91-95, and 110-111 are canceled without prejudice or disclaimer;

(2) claims 130-136 are added; and

(3) claims 6-10, 21-26, 36-41, 66-71, 81-86, 96-101, 106-107, 114-115, 118-119, 122-123, and 126-127 are amended; so that

(4) claims 6-11, 21-26, 36-41, 66-71, 81-86, 96-101, 106-107, 114-115, 118-119, 122-123, 126-127, 130-131, 132-133, and 134-136 are now pending. Claims 6-11, 21-26, 130-131, and 134-136 corresponds to elected subject matter. Claims 36-41, 66-71, 81-86, 96-101, 106-107, 114-115, 118-119, 122-123, 126-127, and 132-133 correspond to non-elected subject matter. Applicant kindly requests that the Examiner rejoin all non-elected claims once the elected claims are considered to be in a condition for allowance (see MPEP 821.04).

The amendments to claims 6-10 are supported on pages 15-17 of provisional application 60/474,368 (hereafter "the priority application"), filed May 30, 2003. The amendments to claims 36-41 are supported on page 1, lines 11-20 of the priority application. The amendments to claims 106-107, 114-115, 118-119, and 122-123 are supported on pages 30-32 of the priority application. New claims 130-136 are supported by the priority application at pages 15-17; page 26, lines 1-5; page 28, lines 11-15; page 1, lines 11-20; and pages 30-32. Other amendments are intended to improve readability and to reflect cancellation of previously pending claims.

No new matter is believed to be added upon entry of the amendment.

Summary of June 19, 2007 Discussion with Examiners McIntosh and Jiang

Applicant thanks Examiners McIntosh and Jiang for conducting the kind and courteous discussion with Applicant's representatives, Daniel R. Evans, Ph.D. and Michael ("Mike") J. Sofia, Ph.D., a representative of Pharmasset, Inc. During the discussion, Drs. Evans and Sofia proposed addressing the claim of priority to the priority application, and provided reasons why claims of the present application are both novel and unobvious over certain references of record. The content of the discussion is reflected in the amendments to the claims and the following remarks.

Priority Claim

Applicant requests that the Examiner acknowledge the timely made claim of priority under 35 U.S.C. § 119(e) to U.S. provisional application 60/474,368 filed May 30, 2003.

Objections to Specification and Claims

Applicant believes that the present amendment obviates all objections to the Specification and Claims. Withdrawal of the objections is respectfully requested.

Rejections of the Claims

The Office has taken the position that:

(1) claims 1-5, 9, 16-20, and 24 are rejected as being non-enabled under 35 U.S.C. § 112, first paragraph because of the breadth of certain claims;

(2) claims 1-11 and 16-26 are rejected as being non-enabled under 35 U.S.C. § 112, first paragraph because of the term "prodrug thereof;"

(3) claims 1-11 and 16-26 are rejected as being indefinite under 35 U.S.C. § 112, second paragraph because of the terms "optionally substituted," "such as," and certain parenthetical terms; and

(4) claims 6-8, 10-11, 21-23, and 25-26 are rejected as being anticipated under 35 U.S.C. § 102(e) by LaColla et al (US 2007/0042939, hereafter "LaColla" or "the LaColla published application") because LaColla discloses at page 57, paras. 420-427, 2'-deoxy-2'-fluoro-2'-methyl-pyrimidine compounds.

Applicant's Traversal of the Rejections of the Claims

As indicated to the Examiners during the June 19, 2007 discussion, the issue to resolve so that all rejections can be withdrawn is the Examiner's objection to the claim to priority to the priority application because withdrawal of this objection obviates all outstanding rejections. The Examiner's attention is directed page 3, lines 1-3, of the March 30, 2007 Office Action in which the Office asserted that claims "1-5, 9, 16-20, and 24 are not entitled to the benefit of the prior application." Applicant notes that implicit to this statement is that at least original claims 6 and 11 are entitled to the benefit of the priority application. Applicant does not concede that the Offices's position is correct; but in order to expedite prosecution, Applicant has amended the claims so that the presently claimed subject matter is supported by the priority application. For example, claims 1-5 are canceled without prejudice or disclaimer and claim 6 is amended so that it is supported by the priority application. Because the presently amended claims, which are believed to be free of certain indefinite language, are supported by the priority application, all of the rejections should be withdrawn.

Applicant takes the position that all of the outstanding rejections are now improper in view of the amendments to the claims, the evidence disclosed in the present application, the evidence presented in the concurrently filed unsigned Declaration of Drs. Furman and Sofia, and the reasoning and legal principles presented below.[1] Accordingly, the rejections of:

(1) claims 1-5, 9, 16-20, and 24 under 35 U.S.C. § 112, first paragraph as being non-enabling because of the breadth of certain claims;

(2) claims 1-11 and 16-26 under 35 U.S.C. § 112, first paragraph, as being non-enabling because of the term "prodrug thereof;"

[1] Applicant intends to file a signed and dated Declaration shortly.

(3) claims 1-11 and 16-26 under 35 U.S.C. § 112, second paragraph, because of the terms "optionally substituted," "such as," and certain parenthetical terms; and

(4) claims 6-8, 10-11, 21-23, and 25-26 under 35 U.S.C. § 102(e) by LaColla et al (US 2007/0042939, hereafter "the LaColla published application") because the LaColla published application discloses at page 57, paras. 420-427, 2'-deoxy-2'-fluoro-2'-methyl-pyrimidine compounds

are obviated by amendment (see rejections (1)-(3)) or respectfully traversed (see rejection (4)).

The rejection of claims 1-5, 9, 16-20, and 24 under 35 U.S.C. § 112, first paragraph as being non-enabling because of the breadth of certain claims should be withdrawn because claims 1-5 and 16-20 are cancelled. The rejection should also be withdrawn because claim 9 is amended so that it falls within the scope of claim 6, which is supported by the priority application. Finally, the rejection should be withdrawn because claim 24 depends on claim 9, which in turn depends on claim 6. Applicant kindly requests withdrawal of this rejection.

The rejection of claims 1-11 and 16-26 under 35 U.S.C. § 112, first paragraph, as being non-enabling because of the term "prodrug thereof" should be withdrawn because this expression does not appear in the presently amended claims. Applicant kindly requests withdrawal of this rejection.

The rejection of claims 1-11 and 16-26 under 35 U.S.C. § 112, second paragraph, because of the terms "optionally substituted," "such as," and certain parenthetical terms should be withdrawn because these terms do not appear in the presently amended claims. Applicant kindly requests withdrawal of this rejection.

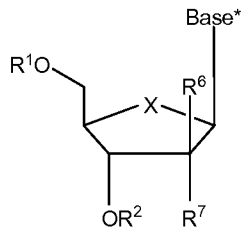
Finally, the rejection of claims 6-8, 10-11, 21-23, and 25-26 under 35 U.S.C. § 102(e) by the LaColla published application is respectfully traversed because the disclosure of the LaColla published application does **NOT** qualify as prior art. Although the LaColla published application discloses at page 57, paras. 420-427, 2'-deoxy-2'-fluoro-2'-methyl-pyrimidine compounds, the effective filing date of this subject matter is June 27, 2003. Because the priority

application of the present application has a filing date that antedates the effective filing date of the subject matter of interest contained in the LaColla published application by about 1-month and because the presently claimed subject matter is entitled to the benefit of the filing date of the priority application, the disclosure of the LaColla published application does **NOT** qualify as prior art. A full appreciation of this position can be gleaned by considering the following facts.

The LaColla published application (see № 5 in Table below) is related to eight other U.S. non-provisional applications. The LaColla published application is a continuing application of 10/608,907, filed June 27, 2003 (see № 4, hereafter "the LaColla parent application" or "the LaColla published parent application"), which claims priority to three provisional applications (see №'s 1-3).

№	Appln No.	Filing Date	Pat/Pub No.	Pub Date
1	60/392,350	Jun 28, 2002	n/a	n/a
2	60/466,194	Apr 28, 2003	n/a	n/a
3	60/470,949	May 16, 2003	n/a	n/a
4	10/608,907	Jun 27, 2003	2007/0087960	Apr 19, 2007
5	11/005,441	Dec 6, 2004	**2007/0032449**	Feb 8, 2007
6	11/005,445	Dec 6, 2004	2007/0042939	Feb 22, 2007
7	11/005,447	Dec 6, 2004	2007/0042991	Feb 22, 2007
8	11/005,467	Dec 6, 2004	2007/0042940	Feb 22, 2007
9	11/005,468	Dec 6, 2004	2007/0027065	Feb 1, 2007
10	11/005,469	Dec 6, 2004	2007/0027104	Feb 1, 2007
11	11/005,470	Dec 6, 2004	2007/0027066	Feb 1, 2007
12	11/005,473	Dec 6, 2004	7,192,936 (2007/0032407)	Mar 20, 2007 (Feb 8, 2007)

The LaColla published application discloses at page 57, paras. 420-427, 2'-deoxy-2'-fluoro-2'-methyl-pyrimidine compounds. This text is found in the LaColla published parent application at page 57, paras. 419-424, which corresponds to the disclosure of the LaColla parent application at page 100, lines 6-29. For convenience the passage of interest is reproduced below, which refers to Formula IX:



(IX)

[0419] X is O, S, SO_2 or CH_2;
[0420] Base* is a purine or pyrimidine base;
[0421] R^{12} is $C(Y^3)_3$;
[0422] Y^3 is independently H, F, Cl, Br or I; and
[0423] R^{13} is fluoro.
[0424] In one subembodiment X is O, and Y^3 is H. In another subembodiment, when X is O and Y is H, R^1, R^2 and R^3 are also H.

Applicant notes that although the LaColla parent application claims priority to the three provisional applications that antedate the priority application of the present invention, **none** of these three provisional applications contain the excerpted passage of the LaColla parent application found at page 100, lines 6-29. Instead, the three provisional applications disclose generic compounds that include a vast number of compounds. Moreover, the three provisional applications do **not** contain an enabling disclosure with respect to the excerpted passage found in the LaColla parent application found at page 100, lines 6-29, and they do not disclose preferred substituents that would allow one to at once envisage the compounds disclosed in the excerpted passage of the LaColla parent application found at page 100, lines 6-26. Consequently, the effective filing date for the aspect of the LaColla published application that the Office has relied on is June 27, 2003. Because Applicant's priority application antedates this subject matter by about one-month, the LaColla published application, as well as the LaColla parent application, does not qualify as prior art under 35 U.S.C. § 102(e). Because neither the LaColla published application nor the LaColla parent application qualify as prior art under 35 U.S.C. § 102(e) this rejection should be withdrawn. But before this conclusion can be made, it is instructive to consider both the relevant case law and the disclosure of the three priority applications.

Applicant notes that the law of anticipation applicable for the present matter is found at MPEP 2131.02, which succinctly states in a sub-heading that "a generic chemical formula will

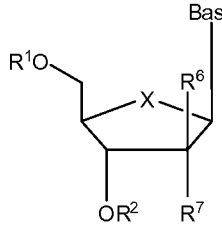
anticipate a claimed species covered by the formula when the species can be "at once envisaged" from the formula." In particular, the Examiner's attention is directed the fourth full paragraph of MPEP 2131.02, which is reproduced below with bold-type emphasis supplied:

> In *In re Petering*, the prior art disclosed a generic chemical formula "wherein X, Y, Z, P, and R"- represent either hydrogen or alkyl radicals, R a side chain containing an OH group." **The court held that this formula, without more, could not anticipate a claim to 7-methyl-9-[d, l"-ribityl]-isoalloxazine because the generic formula encompassed a vast number and perhaps even an infinite number of compounds.** However, the reference also disclosed preferred substituents for X, Y, Z, R, and R" as follows: where X, P, and R" are hydrogen, where Y and Z may be hydrogen or methyl, and where R is one of eight specific isoalloxazines. The court determined that this more limited generic class consisted of about 20 compounds. The limited number of compounds covered by the preferred formula in combination with the fact that the number of substituents was low at each site, the ring positions were limited, and there was a large unchanging structural nucleus, resulted in a finding that the reference sufficiently described "each of the various permutations here involved as fully as if he had drawn each structural formula or had written each name." The claimed compound was 1 of these 20 compounds. Therefore, the reference "described" the claimed compound and the reference anticipated the claims.
>
> See *In re Petering*, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

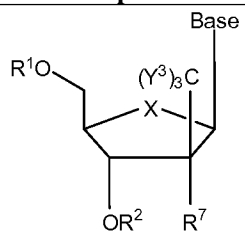
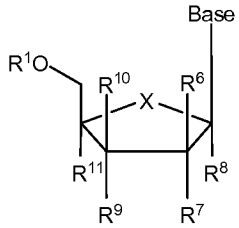
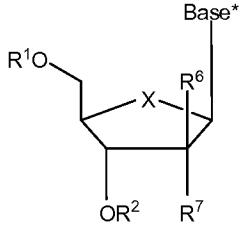
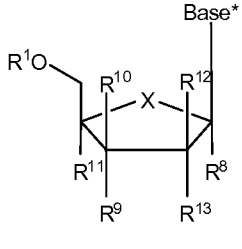
Applicant notes that the facts of the present matter fall squarely within the holding of the *Petering Court* insofar that the question is whether a generic compound that contains a "vast number…of compounds," without more, anticipates a compound (or in the present matter a few selected compounds). So as one considers the disclosures of the three provisional applications, the underlying question is whether the generic compounds, when viewed in light of other information contained therein, would allow one to "at once envisage" not only the aspect of the LaColla parent application but the claimed compounds. After a review of the three provisional applications, Applicant believes that the Examiner will appreciate that these three applications disclose generic compounds that include a vast number of compounds, but they do not disclose preferred substituents that would allow one to "at once envisage" the presently claimed compounds.

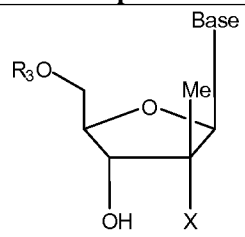
As indicated above, the LaColla parent application claims priority to the following U.S. provisional applications: 60/392,350 ("the '350 application"), 60/466,194 ("the '194 application"), and 60/470,949 ("the '949 application). The '350 application containing 5,200+ pages discloses generic compounds useful for treating Flaviviridae. Certain aspects of this application are considered in greater detail below. The '194 application discloses improved synthetic procedures for preparing certain nuclesides, such as, β-D-2'-C-methyl-cytidine (see the '194 application at Fig. 3). This compound is outside the scope of the presently claimed subject matter. Indeed, Applicant provides data in the disclosure of the present application that compares one of the presently claimed compounds to β-D-2'-C-methyl-cytidine (see discussion below). The '949 application, like the '350 application, discloses generic compounds that embrace a vast number of compounds; but there is no specific recitation of the passage that appears in the LaColla parent application. In view of these disclosures, Applicant believes that the relevant disclosure to consider is the '350 application, which does not disclose the excerpted passage present in the LaColla parent application, and thus, does not anticipate the claimed invention.

The following Table summarizes the compounds that Applicant believes are relevant for the present matter.

№	Compound	Citation (Page, lines)	Comment
1	 (IV)	(15, 9-14) (48, 1-5)	Third principle embodiment Genus size includes a vast number of compounds.[2] Base **excludes** presently claimed bases. First, second, and third subembodiments for (IV) disclosed on pp. 56-58 are directed to non-natural bases because W^4 is CX^3 and X^3 is CH_3, CF_3, or CH_2CH_3.

[2] Genus size for entry number 1 estimated to include 1 x 10^{100} compounds. Genus size estimated by finding the product of the number of possible substituents for each of the radicals (R^1, R^2, R^6, R^7, X, and Base). For example, R^1 is defined on page 45, lines 8-20, is estimated to include at least 473 possible substituents, while Base (A) alone, found on page 48, represents a sub-genus that is estimated to include at least 7.2 x 10^{14} members. For R^1, the number of substituents is estimated by considering specific and general substituent recitations. The general substituents are defined on pages 104-107 of the '350 application.

№	Compound	Citation (Page, lines)	Comment
	 (IV)	(57, 15-26)	Preferred subembodiment of entry number 1. Sub-genus size includes a vast number of compounds. Base "is as defined herein" (see pp. 48-54, especially definition for X^3 on page 54) **excludes** presently claimed bases.
2	 (VI)	(24, 5-10) (58, 18-22)	Fourth principle embodiment. Genus size includes a vast number of compounds.[1] Aspects of preferred embodiments disclosed on pp. 60-76 include: (i) pp. 60-62 embraces a vast number of compounds; (ii) pp. 62-64 excludes presently claimed compounds because R^6 and R^7 come together to form a spiro compound; (iii) pp. 64-66 embraces a vast number of compounds; (iv) pp. 66-68 excludes presently claimed compounds because R^6 and R^7 come together to form a spiro compound; and (v) pp. 68-76 compounds exclude presently claimed compounds because X is a carbon based radical. Aspects of preferred subembodiments disclosed on pages 84-90 include: (i) all compounds **exclude** substituent at R^7 being F (*see* p. 84, ll. 18-20; p. 85, l. 4 and ll. 19-21; p. 86, ll. 2-4, ll. 17-18, and ll. 31-33; p. 87, ll. 13-15 and ll. 30-31; p. 88, ll. 14-15 and 28-30; p. 89, l. 4, ll. 10-11, ll. 16-17, ll. 22-24, and ll. 30-31; and p. 90, ll. 1-24. General methods for preparing 2'-C-branched nucleosides appear at page 117.
3	 (IX)	(26, 1-6) (91, 1-6)	Fifth principle embodiment Genus size includes a vast number of compounds.[1] Unlike other principle embodiments, the '350 application does not disclose certain preferred embodiments and subembodiments of the principle embodiment.
4	 (XI)	(27, 15-20) (92, 15-20)	Sixth principle embodiment. Genus size includes a vast number of compounds.[1]

№	Compound	Citation (Page, lines)	Comment
5	 (XIX)	(32, 1-5) (97, 1-5)	Fourth particular aspect (see pp. 97-99). Genus size includes a vast number of compounds. The '350 aplication discloses that the base "is a non-natural base selected from the group of…(see structures on page 98, which taking into account various substituents accounts for at least 12,000 different bases).

The remainder of the '350 application, see pages 98ff, is directed to definitions, general synthetic procedures, extensive tabular listings of contemplated species, as well as, some activity data. Applicant believes that the '350 application does not anticipate the presently claimed subject matter because one would not at once envisage the excerpted passage found in the LaColla parent application. Applicant believes that the same conclusion can be made for the other two provisional applications. Applicant would also like to note that **none** of the three provisional applications disclose or suggest methods of preparing the presently claimed compounds.

The conclusion to be gleaned then is that none of the three provisional applications, to which the LaColla parent application claims priority to, contain the passage contained in the Lacolla parent application. Applicant believes these three references do not qualify as anticipatory disclosures for the presently claimed subject matter. Consequently, Applicant believes the effective filing date for the aspect of the LaColla published application that the Office has relied upon is June 27, 2003. Because Applicant's priority application antedates this subject matter by about one-month, the LaColla published application, as well as the LaColla parent application, does not qualify as prior art under 35 U.S.C. § 102(e).

Applicant kindly requests that the Examiner acknowledge the same and withdraw this rejection.

Evidence and Reasoning Provided in Support of Nonobviousness

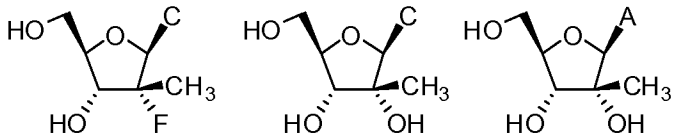
As to the issue of obviousness, Applicant believes that the presently claimed subject matter is unobvious over the LaColla parent and published applications at least for the following reasons.

The (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine compound, as evidenced by the HCV Replicon Assay disclosed in Example 5 on pages 85-86 of the present application, **shows exceptional anti-flavivirus activity**. Example 5 of the present application reads as follows with bold-type emphasis supplied:

> The anti-flavivirus activity of the compounds was determined as described by Stuyver, et al. ("Ribonucleoside analogue that blocks replication of bovine viral diarrhea and hepatitis C viruses in culture", Antimicrobial Agents and Chemotherapy 47:244-254 (2003)). The compound was dissolved in DMSO and added to the culture media at final concentrations ranging from 3 to 100 μM. A 4-days incubation resulted in dose-dependant reduction of the replicon HCV RNA (Figure 1A). **A 1-log reduction of replicon RNA (or EC_{90} value) was reached at approximately 2.5 μM.** Measurement of the reduction of rRNA gave an indication of the inhibitory effect on cellular polymerases. Subtraction of this cellular toxicity value from the antiviral values resulted in the therapeutic index line and EC_{90} value. Based on these calculations, an average EC_{90} value, corrected for cellular toxicity, of approximately 2.5 μM was obtained. Figure 1A shows the dose-dependant reduction of the replicon HCV RNA based on the treatement with (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine. The viral reduction was compared to the reduction of cellular RNA levels (ribosomal RNA) to obtain therapeuric index values. EC_{90} represents the effective concentration 90% at 96 hours following the dose dependant administration of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine. Figure 1B shows the prolonged reduction in replicon HCV RNA up to 7 days following treatment with 5 and 25 μM.

Additionally, the (2'R)-2'-deoxy-2'-fluoro-2'-C-methyl cytidine compound **shows exceptional anti-viral activity and exceptionally low mitochrondial and cellular toxicity**, as evidenced by the data presented in Tables 1-7 on pages 88-91 of the present application (see also pages 32-34 of the published application (US 2005/0009737)). This information is reproduced below for convenience.

For instance, the activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine in the replicon system is summarized in Table 1 and should be compared to the activities found for both 2'-C-methylcytidine (*cf.* discussion above concerning the '194 application and synthesis of 2'-C-methylcytidine at Fig. 3) with and 2'-C-methyladenosine; the structures of each compound are shown below for reference:



A **B** **C**

where: **A**: (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine,
B: 2'-*C*-methylcytidine, and
C: 2'-*C*-methyladenosine.

The EC_{90} values for (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine as well as 2'-*C*-methylcytidine and 2'-*C*-methyladenosine are shown for three separate replicon clones (HCV-WT (Wild Type), 9-13 and 21-5) as well as the S282T mutant replicon. The EC_{90} values for (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine were in the range of 1.6 to 4.6 μM for the replicon clones. In contrast the EC_{90} values for 2'-*C*-methylcytidine were in the range of 6.6-37.4 μM. Interestingly, the EC_{90} values for 2'-*C*-methyladenosine were comparable to those of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine. Neither (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine nor 2'-C-methylcytidine showed toxicity toward the replicon cells, CC50 for rRNA >100μM (Table 1). However, 2'-C-methyladenosine did show cytotoxicity with a CC50 of 38 μM (Table 1). The activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine and 2'-*C*-methylcytidine in three other replicons tested is shown in Table 2. Additionally, no cytotoxicity to these replicon cells was observed with either (2'R)-2'-deoxy-2'-fluoro-2'-C-methylcytidine or 2'-C-methylcytidine (Table 2; IC_{90} for HGPDH >100 μM and IC_{90} in the MTT assay >100 μM).

Table 1: Summary of the Anti-HCV Replicon Activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine*

	(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine	2'-*C*-methylcytidine	2'-*C*-methyladenosine
HCV-WT	4.6 ± 2.0	21.9 ± 4.3	2.1 ± 0.27
S282T	30.7 ± 11.7	37.4 ± 12.1	>100
9-13	4.6 ± 2.3	13.0	0.7
21-5	1.6 ± 0.7	6.6	0.6
rRNA**	>100	>100	38

*Values represent EC_{90} (μM)
**Cytotoxicity in replicon cell line CC_{50}

Table 2: Activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine and 2'-*C*-methylcytidine in other Replicons

	(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine			2'-C-methylcytidine		
Replicon	EC_{90} (μM)	IC_{90} (μM)		EC_{90} (μM)	IC_{90} (μM)	
		GAPDH	MTT		GAPDH	MTT
1b (Ntat)	3.8	>100	>100	27.2	>100	>100
1b (Btat)	11.5	>100	>100	31.1	>100	>100
1a (pp1aSI-7)	34.7	>100	>100	35.0	>100	>100

Table 3 shows the potency of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine-5'-triphosphate (TP) in the NS5B polymerase assay. The inhibitory concentration 50% was determined to be in the range of 1.7 to 7.7 μM.

Table 3: HCV 1b NS5B Polymerase Assay (IC_{50}, μM)

	(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine TP	2'-*C*-methylcytidine TP	2'-*C*-methyladenosine TP
Wild-Type NS5B	1.7 ± 0.4[a] 7.7 ± 1.2[b]	6.0 ± 0.5	20.6 ±5.2
S282T	2.0[a] 8.3 ± 2.4[c]	26.9 ± 5.5	>100

[a] Values determined using batch 1; [b] Value determined using batch 2 and 3; and [c] Value determined using batch 2.

Table 4 shows the range of antiviral activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine. The data shows that, in addition to HCV virus, (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-

methylcytidine shows activity against Rhinovirus, West Nile virus, Yellow Fever virus, and Dengue virus.

Table 4: Summary of Antiviral Activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine

Virus	Cell	EC_{50}, CPE (μM)	EC_{50}, NR[a] (μM)	CC_{50}, CPE (μM)	CC_{50}, NR[a] (μM)
West Nile	Vero	32	12	>100	32
Dengue Type 2	Vero	32/55	>100/>100	>100	>100
Yellow Fever	Vero	19/3.2	32/12	>100	>100
Influenza A (H1N1)	MDCK	>100	>100	>100	>100
Influenza A (H3N2)	MDCK	>100	>100	>100	>100
Influenza B	MDCK	>100	>100	>100	>100
Rhinovirus Type 2	KB	25	20	>100	>100
VEE	Vero	>100	>100	>100	>100
SARSCoV	Vero	>100	>100	>100	>100

[a]NR = Neutral Red.

Table 5 shows the lack of activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine on BVDV, which is typically used as a surrogate model for HCV, as well as other viruses including HIV, HBV and Corona virus. In contrast, 2'-*C*-methylcytidine and 2'-*C*-methyladenosine show greater activity in the HCV surrogate model, BVDV. These results show the necessity for screening this series of compounds against the HCV replicon system versus surrogate HCV systems.

Table 5: Summary of Antiviral Activity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine

Virus	(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine (EC_{90}, μM)	2'-*C*-methylcytidine (EC_{90}, μM)	2'-*C*-methyladenosine (EC_{90}, μM)
BVDVncp	>22	0.5	1.2
BVDVcp	>100	2	1.5
RSV	>100	>100	>100
HIV[a]	>100	ND	ND
HBV	>10	>10	ND
Coronavirus 229E	>100	ND	ND

ND = Not determined.

A summary of the toxicity data for (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine is shown in Tables 6 and 7. Table 6 shows a cytotoxicity analysis in various cell lines (Clone A, Huh7, HepG2, MDBK, PBM, CEM, Vero, MRC-5). Cytotoxic concentration 50% (CC_{50}) was greater than 75-100 μM in all clones tested for (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine as well as 2'-*C*-methylcytidine. In contrast is the relative toxicity of 2'-*C*-methyladenosine. Table 7 shows the lack of effects of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine and 2'-*C*-methylcytidine on mitochondrial DNA synthesis and lack of effects on lactic acid increase in this assay. Results shows the relative lack of toxicity of (2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine.

Table 6: Cytotoxicity Studies[a]

Cell Line	(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine CC_{50}, μM	2'-*C*-methylcytidine CC_{50}, μM	2'-*C*-methyladenosine CC_{50}, μM
CloneA	>100	>100	37
Huh7	>100	>100	30
HepG2	75	>100	58
MDBK	>100	>100	
PBM	>100		
CEM	>100		
Vero	>100		
MRC-5	>100		

[a]Results determined using MTS assay.

Table 7: Mitochondrial Toxicity Study

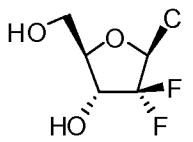
Compound	mtDNA Synthesis (IC_{50}, μM)	Lactic Acid Increase
(2'*R*)-2'-deoxy-2'-fluoro-2'-*C*-methylcytidine	>25	No effect ≥ 33 μM
2'-*C*-methylcytidine	>25	No effect ≥ 33 μM

The data disclosed in the present application provides unexpected results in support of the presently claimed compounds, and therefore, weighs in favor of the conclusion that the presently claimed invention is unobvious over the LaColla published application.

Additional Evidence and Reasoning Supporting Nonobviousness

During the June 19, 2007 discussion referenced above, Examiners McIntosh and Jiang asked why one of ordinary skill would not have been inclined to combine the substituents disclosed in the three provisional applications so as to arrive at the present arrangement of a nucleoside containing C-2'-β-methyl-α-fluoro based on the information available to one of ordinary skill.

In response, Applicant notes that the structure-activity (or structure-cytotoxicity) relationship (SAR) in nucleosides is unpredictable at best. In other words, just because one can mentally prepare molecules having a certain stereochemical arrangement of atoms, does not necessarily mean that the prepared molecules will have useful properties. The following Table represents data that has been obtained under the supervision and/or direction of Declarants Phillip Furman, Ph.D. and Michael J. Sofia, Ph.D., both employed by Pharmasset, Inc., the assignee of the present application, and is provided in the form of a unsigned Declaration that is filed concurrently herewith (see footnote 1 at page 25). In particular, Declarants' data provides for a comparison of the effect of substitution at the 2'-position of the furanosyl moiety for the following compounds.



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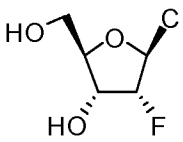

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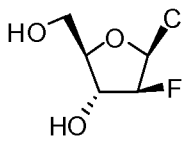

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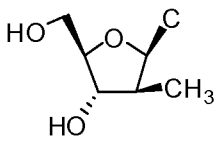

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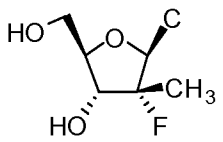

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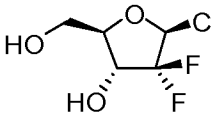
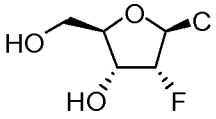
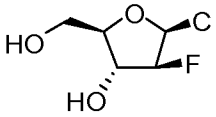
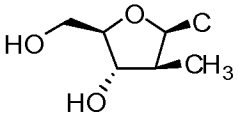
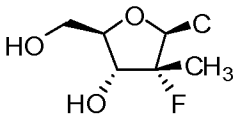
Specifically, Declarants' data serves to illustrate that substitution at the 2'-furanosyl position can have a substantial impact on the anti-viral activity and/or cytotoxicity.

Activity and Cytotoxicity Comparison of 2' Substituted Cytidine Analogs

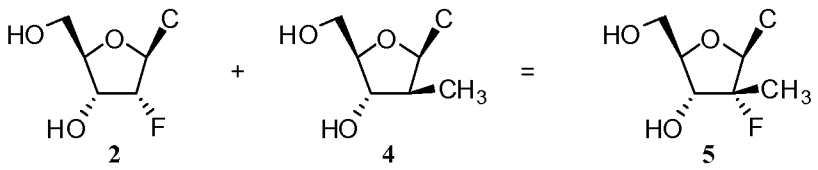
№	Compound	HCV Activity EC_{90} (μM)	Cytotoxicity Clone A CC_{50} (μM)	Hep G2 CC_{50} (μM)	BxPC3 CC_{50} (μM)	CEM CC_{50} (μM)
1		<1	<0.1	<1	<1	<1
2		5.66	>100	400	10	6
3		Can not determine: Toxic to cells	<50	200	5	5
4		9.73	10.47	40	<1	<1
5		4.5	>100	>1000	>1000	>1000

C represents cytosine.

Compound **1**, gemcitabine, which is marketed under the tradename Gemzar®, shows anti-viral (HCV) activity (90% effective concentration (EC90) < 1 μM), but shows marked cytotoxicity for each of the designated cell lines (Clone A, Hep G2, BxPC3, and CEM). Compounds **2** and **4** show different degrees of anti-viral activity, but also show a varied degree of cytotoxicity. The HCV activity of compound **3** is unmeasurable because it is too toxic for cells. All of these data, should be contrasted to the data obtained for compound **5**, i.e., (2'*R*)-2'-

deoxy-2'-fluoro-2'-*C*-methylcytidine, which is the subject matter of claim 11, showing anti-HCV activity and substantially no cytoxicity for each of the four cell lines.[3]

Applicant believes that an answer to the question posed by Examiners McIntosh and Jiang during the June 19, 2007 discussion is that it would not have been obvious to try the presently claimed compound from the information disclosed in the three provisional applications of the LaColla parent application and from information based on knowledge of one of ordinary skill because the SARs for these compounds are not necessarily correlative with one another. In other words, one would expect that a compound that has a β-methyl and an α-fluoro would have properties akin to the combined properties of compounds **2** and **4**.



Inspection of the data above clearly shows that this is not the case because compound **5** is both more active and less cytotoxic than either one of compounds **2** and **4**. Applicant believes that this result is truly unexpected and provides yet another reason why the presently claimed invention is unobvious over information contained in the disclosure of the three provisional applications of the LaColla published application and from information based on knowledge of one of ordinary skill.

In view of the facts of record, the evidence provided in the disclosure of the present application, the evidence provided by way of the unsigned Declaration Under 37 CFR 1.132 filed concurrently herewith (see footnote 1 at page 25), and the reasoning that flows from the same, Applicant believes that every aspect of the the presently claimed invention is both novel and

[3] Both Declarants and Applicant are aware that the reported cytotoxicty value of Hep G2 (CC50) of > 1000 μM provided in the Table above (see concurrently filed Declaration) is different than the reported cytotoxicty value of Hep G2 (CC50) data of 75 μM presented in Table 6 of the present application. Upon consideration, Applicant notes that the data present in application Table 6 was generated in a different lab at a different location by different staff and so the variation in technique and environment may be different than that used to generate the data presented in the concurrently filed Declaration. The Declaration data for all the compounds were generated under current standard conditions and are internally consistent, demonstrating the lack of cytotoxicity of the substituents at the 2'-position.

unobvious over the LaColla published application, the LaColla parent application, and the three provisional applications of the LaColla parent application.

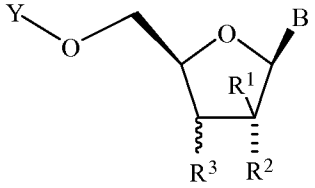
Applicant kindly requests that the Examiner: (1) acknowledge that claims 6-11 are novel and unobvious over the cited references of record; (2) allow these claims and all active claims dependent thereon; (3) rejoin and allow the withdrawn claims that depend directly or indirectly on claims 6 and 11; and (4) allow new claims 130-136 based on reasoning presented above.

Consideration of U.S. Patent No. 7,105,499

During the June 19, 2007 discussion, Applicant's representative brought to the Examiner's attention the disclosure of U.S. Patent No. 7,105,499, which is of record, and provided reasons why the presently claimed invention was both novel and unobvious over this disclosure.

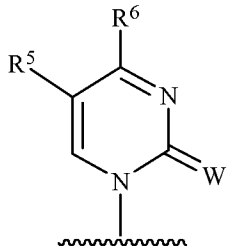
The '499 patent contains two claims which are reproduced below:

> 1. A method of treating hepatitis C virus (HCV) infection comprising administering to a mammal in need of such treatment a therapeutically effective amount of a compound of structural formula III, or a pharmaceutically acceptable salt or acyl derivatives thereof,



(III)

wherein B is



W is O or S;
Y is H, $C_{1\text{-}10}$ alkylcarbonyl, $P_3O_9H_4$, $P_2O_6H_3$, or $P(O)R^9R^{10}$;
R^1 is CF_3, or $C_{1\text{-}4}$ alkyl and one of R^2 and R^3 is OH or $C_{1\text{-}4}$ alkoxy and the other of R^2 and R^3 is fluoro;

R^6 is H, OH, SH, NH_2, C_{1-4} alkylamino, di(C_{1-4} alkyl)amino, C_{3-6} cycloalkylamino, halogen, C_{1-4} alkyl, C_{1-4} alkoxy, or CF_3;

R^5 is H, C_{1-6} alkyl, C_{2-6} alkenyl, C_{2-6} alkynyl, C_{1-4} alkylamino, CF_3, or halogen; and

R^9 and R^{10} are each independently hydroxy, $OCH_2CH_2SC(=O)$t-butyl, or $OCH_2O(C=O)$iPr.

2. The method of claim 1 wherein a compound of structural formula III, or a pharmaceutically acceptable salt or acyl derivatives thereof is in combination with a therapeutic amount of another agent active against HCV infection selected from the group consisting of ribavirin; levovirin; thymosin alpha-1; an inhibitor of NS3 serine protease; an inhibitor of inosine monophosphate dehydrogenase; and interferon-α or pegylated interferon-α.

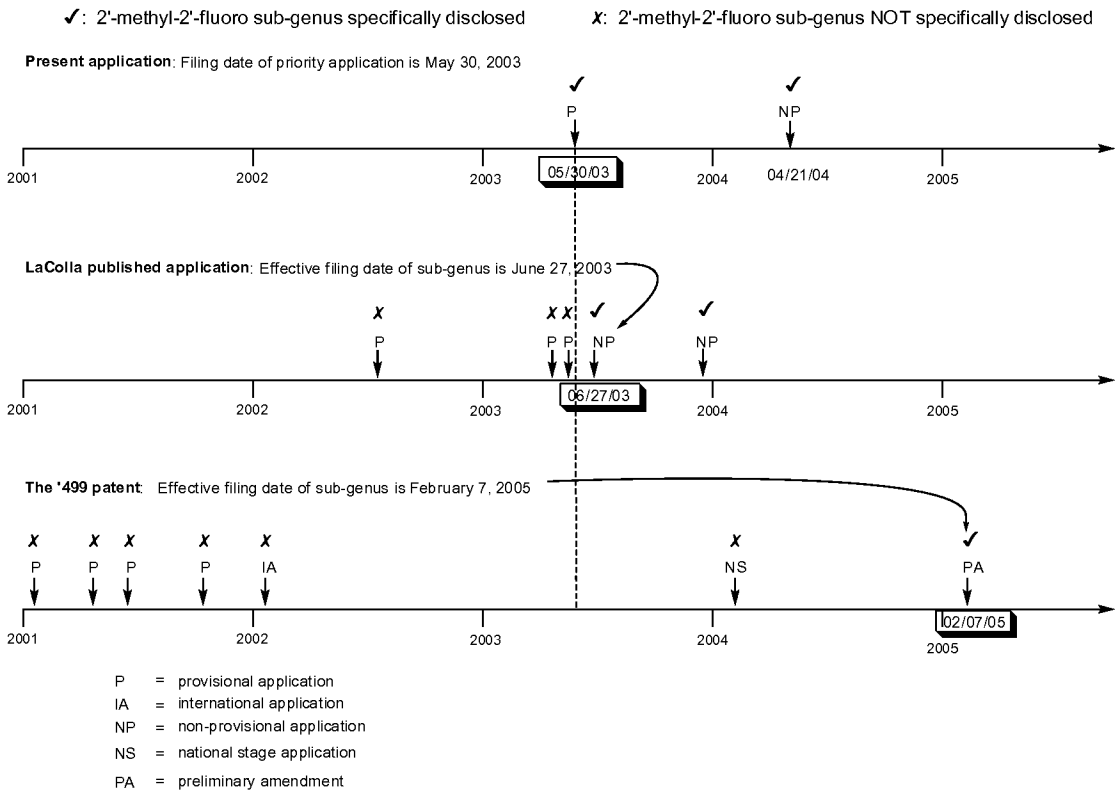
The '499 patent issued September 12, 2006 from a national stage application based on an international application (PCT/US02/01531), filed January 18, 2002, which published as WO 02/057425 on July 25, 2002. The '499 patent claims priority to four U.S. Provisional applications: 60/344,528, filed October 25, 2001, 60/299,320 filed June 19, 2001, 60/282,069 filed April 6, 2001 and 60/263,313 filed January 22, 2001.

Athough the '499 patent is based on an application that has a filing date that antedates the priority application of the present application, Applicant believes that there is no issue of anticipation under 35 U.S.C. § 102(e) for substantially the same reasoning as that applied to the LaColla published application. In other words, although the '499 patent application discloses a nucleoside genus that contains a vast number of compounds, there is no disclosure contained in the '499 patent or its respective priority applications that would allow one to once envisage the present claimed compounds. Indeed, Applicant notes that the first occurance of the method of treating claims that includes the recited nucleoside sub-genus of claims 1-2 of the '499 patent did not appear until applicants of the '499 patent filed a Preliminary Amendment on **February 7, 2005**. In the February 7, 2005 amendment, the '499 patent applicant canceled claims directed to a generic compound containing a vast number of compounds (see claims 42-52), and added new claims 53-54, which ultimately issued after amendments as claims 1-2 of the '499 patent.

Accordingly, Applicant believes that for purposes of novelty and unobviousness, the effective filing date of the claims of the '499 patent is **February 7, 2005**. Because the priority application of the present application antedates the effective filing date of the sub-genus claimed in the '499 patent, Applicant believes that the '499 patent does not qualify as prior art. As for the disclosure of the '499 patent itself, there is no issue of anticipation because one of ordinary skill would not have "at once envisaged" the recited sub-genus as recited in claims 1-2 from the vast number of compounds disclosed at cols. 3-9 of the '499 patent. As for obviousness, Applicant believes that the evidence of record adequately shows the unobviousness of the presently claimed invention. Applicant requests that the Examiner acknowledge the same.

Summary

The presently claimed invention is novel over the subject matter of both the LaColla published application (see page 57, paras. 420-427) and the '499 patent (see claims 1-2) because the effective filing date of the present application antedates the "effective filing" dates of both the LaColla published application and the '499 patent, as evidenced by the following diagram.



In other words, although both the LaColla published application and the '499 patent disclose a sub-genus that is similar to the presently claimed subject matter, this subject matter did not appear until June 27, 2003 (the filing date of the LaColla parent application) and February 7, 2005 (the filing date of a Preliminary Amendment (PA) for the '499 patent). Because both the priority applications of the LaColla published application and the international and priority applications of the '499 patent do not disclose or suggest this sub-genus with sufficient specificity, the effective filing dates for the sub-genus subject matter of the the LaColla published application and the '499 patent are June 27, 2003 and February 7, 2005, respectively. Because the presently claimed application is entitled to receive the full benefit of the priority application filed May 30, 2003 and because this filing date antedates the effective filing dates of both the LaColla published application and the '499 patent, neither the LaColla published application nor the '499 patent are available as prior art for purposes of an anticipatory rejection.

The presently claimed subject matter is unobvious over the generic disclosures of the LaColla published application and the '499 patent because one would not expect, at least based on the vast number of compounds disclosed both in the three provisional applications of the LaColla published application and international and provisional applications of the '499 patent, that a nucleoside having a 2'-C-β-methyl-α-fluoro configuration, as presently claimed, would exhibit such high anti-viral activity **and** such low cytotoxicity. For at least this reason, Applicant believes that the presently claimed compounds, compositions, and methods for using and making the same are unobvious over both the above-indicated references.

Applicant requests that the Examiner conclude the same and formally withdraw the Office's previous position concerning the patentability of the pending claims and pass the present application to issue. The Examiner is invited to contact Applicant's undersigned representative in the event the Examiner finds the need to do so. In the event that Applicant owes a fee that has not yet been paid, Applicant requests that the Office charge any additionally required fees to deposit account no. 13-2725.

23552
PATENT TRADEMARK OFFICE

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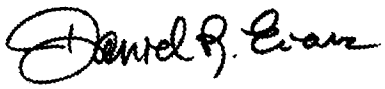

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